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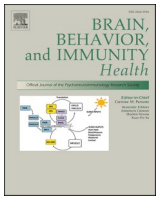

Neuroimmune modulators as novel pharmacotherapies for substance use disorders

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ABSTRACT

One promising avenue of research is the use of neuroimmune modulators to treat substance use disorders (SUDs). Neuroimmune modulators target the interactions between the nervous system and immune system, which have been found to play a crucial role in the development and maintenance of SUDs. Multiple classes of substances produce alterations to neuroimmune signaling and peripheral immune function, including alcohol, opioids, and psychostimulants Preclinical studies have shown that neuroimmune modulators can reduce drug-seeking behavior and prevent relapse in animal models of SUDs. Additionally, early-phase clinical trials have demonstrated the safety and feasibility of using neuroimmune modulators as a treatment for SUDs in humans. These therapeutics can be used as stand-alone treatments or as adjunctive. This review summarizes the current state of the field and provides future directions with a specific focus on personalized medicine.

1. Introduction

Substance use disorders (SUDs) are a major public health concern and novel pharmacotherapies are urgently needed to combat this epidemic. SUDs are chronic, relapsing disorders, characterized by intermittent drug use which transitions to continued use despite negative consequences (Koob and Volkow, 2016). In the United States, over 46 million people (16.5% of the population) met criteria for a past-year SUD (Abuse, 2022). Alcohol was the most commonly used substance, with the majority of individuals (29.5 million) having met criteria for an alcohol use disorder (AUD) (Abuse, 2022). Critically, it is estimated that 94% of people with an SUD did not receive any treatment (Abuse, 2022), in part because of the lack of efficacious pharmacotherapies to treat these disorders. Other contributing factors to the low treatment rates include stigma, lack of access to health care, and lack of trained SUD providers (Farhoudian et al., 2022).

One promising avenue of research is the use of neuroimmune modulators to treat SUDs. Neuroimmune modulators target the interactions between the nervous system and immune system, which have been found to play a crucial role in the development and maintenance of SUDs (Crews et al., 2017; Lacagnina et al., 2017; Linker et al., 2019). Multiple classes of substances produce alterations to neuroimmune signaling and peripheral immune function, including alcohol, psychostimulants, and opioids (Crews and Vetreno, 2016; Hofford et al., 2019; Meredith et al., 2021).

In brief, the neuroimmune system consists of brain cells that are responsive to threats in the neuronal environment. The resident immune cells in the brain are microglia and astrocytes, which release immune signals in response to threats (Dantzer, 2018). During an initial immune activation, inflammatory responses are triggered by pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS). Toll-like receptors (TLRs) sense PAMPs and induce intracellular-signaling cascades, such as nuclear factor-κB (NF-κB) interferon (IFN) response, and cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), to cause an inflammatory response (Tartey and Takeuchi, 2017). The inflammatory response is driven by cytokines, which are small immune proteins, which are released by immune cells to coordinate immune responses between cells in the periphery and brain (Becher et al., 2017). Chronic inflammation is caused by dysregulation of cytokine networks, which has been found in neuropsychiatric disorders, including AUD and SUDs ((Crews et al., 2017; Hofford et al., 2019) see Figs. 1 and 2).

Preclinical studies have shown that neuroimmune modulators can reduce drug-seeking behavior and prevent relapse in animal models of

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SUDs (Bell et al., 2015; Snider et al., 2013b; Theberge et al., 2013). Additionally, early-phase clinical trials have demonstrated the safety and feasibility of using neuroimmune modulators as a treatment for SUDs in humans (Meredith et al., 2021). This short narrative review will briefly summarize the current state of the field and provide future directions with a specific focus on personalized medicine.

2. Alcohol

A host of preclinical and clinical studies have evaluated immune therapies for AUD (see Table 1). In brief, alcohol alters neuroimmune signaling indirectly by initiating systemic production of proinflammatory cytokines and directly by the release of inflammatory molecules in the brain (Crews and Vetreno, 2016).

2.1. Toll-like receptors (TLRs) targets for AUD

Studies investigating the neuroimmune modulation of TLRs for AUD have been largely preclinical. The majority have studies have found that TLR4 blockade by naltrexone, nalmefene, and novel compounds, reduces ethanol intake, preference, and binge-drinking (Bajo et al., 2016; Jacobsen et al., 2018; Montesinos et al., 2017). Clinical studies with these compounds have not focused on their neuroimmune mechanisms, but have found improvements in drinking outcomes. Preclinical findings with other TLR modulators, such as amlexanox, a TLR3/TRIF inhibitor, have found reductions in ethanol consumption and preference (McCarthy et al., 2018).

2.2. Peroxisome proliferator-activated receptor (PPAR) targets for AUD

Initial preclinical studies of PPARagonists were promising, with consistent findings of reduced ethanol intake, preference, self-administration, and ethanol-induced reinstatement (Blednov et al., 2015, 2016; Fotio et al., 2021; Karahanian et al., 2014; Ozburn et al., 2020; Stopponi et al., 2011). However, translation to clinical samples has been disappointing. An unpublished Phase II clinical trial of fenofibrate, a PPARα agonist, found minor improvements in alcohol craving and drinking (NCT02158273). Two other studies testing a PPARγ agonist (piaglitazone) for AUD were terminated early (NCT03539432; NCT01631630); with one termination due to concern over increased risk for myopathy in the active treatment group (Schwandt et al., 2020). Moreover, there are concerns related to the long-term side effect profiles of PPARγ agonists (Amato and Neves, 2012; Wright et al., 2014). Despite these concerns, there is an ongoing clinical trial of pioglitazone for AUD in veterans (NCT03864146).

2.3. Microglia and astrocyte targets for AUD

Studies targeting microglia for AUD have been mixed. Studies have shown a benefit of minocycline, a microglial attenuator, in reducing alcohol intake, withdrawal-related anxiety, and alcohol-induced reinstatement (Agrawal et al., 2011; Gajbhiye et al., 2018). However, these effects may be non-specific as minocycline reduced both alcohol and water intake in mouse models (Lainiola and Linden, 2017). The only clinical trial of minocycline for AUD found no benefit of active treatment over placebo on the subjective response to alcohol, alcohol craving, or serum cytokine levels (Petrakis et al., 2019). A number of pharmacotherapies targeting astrocytic glutamate transporter 1 (GLT-1), which aids in the regulation of extracellular glutamate, have been evaluated for AUD (Fig. 1). Preclinical studies with N-acetylcysteine (NAC), an antioxidant precursor to glutathione, have shown promise; NAC reduces ethanol seeking and self-administration (Lebourgeois et al., 2018) and

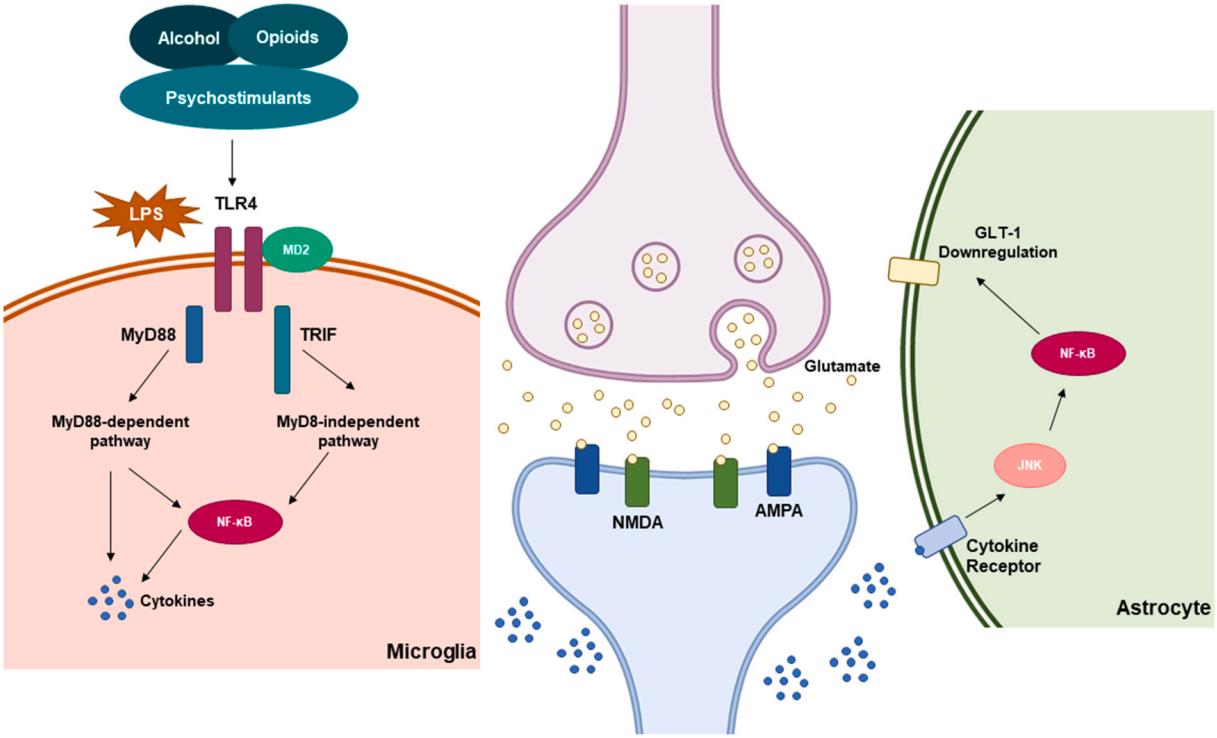

Fig. 1. TLR and Glutamate Pathways
Alcohol, opioids, and psychostimulants activate TLR4, and TLR4's co-receptor MD-2 on microglia. TLR4 activation induces a signaling cascade through the MyD88-depedent pathway, which results in the activation of NF- κB. Microglia then release pro-inflammatory cytokines, which bind to their receptors on astrocytes and activate NF- κB through c-Jun N-terminal kinase (JNK) pathways. This ultimately results in the downregulation of the GLT-1 transported, which causes the astrocyte to be unable to clear excess glutamate from the synapse. Substances and substance cues cause glutamate release from cortical afferents in the striatum, which leads to the activation of glutamate receptors (AMPA and NMDA), and induces post-synaptic plasticity. TLR4 = Toll-like receptor 4; NF- κB = nuclear factor-kappe B; GLT-1 = Glutamate transporter 1; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA = N-methyl-D-aspartic acid.

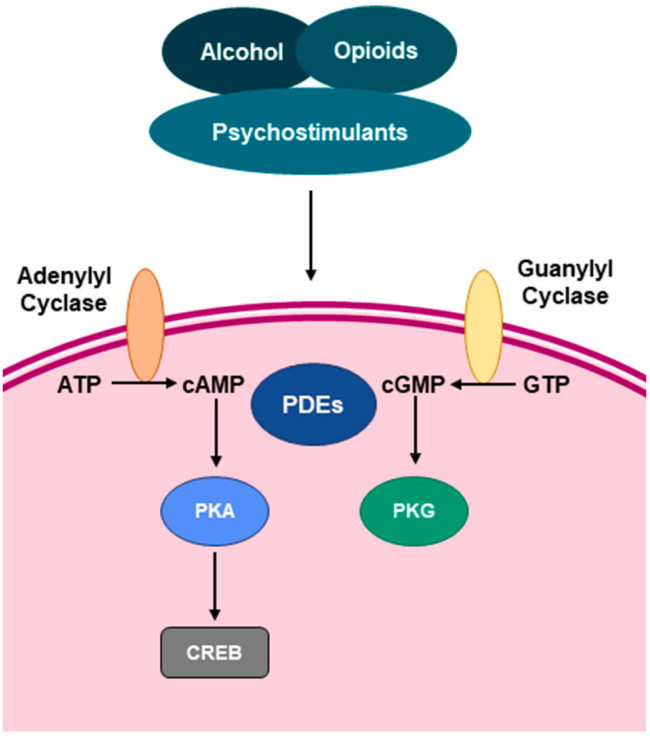

Fig. 2. CREB Pathway
Adenylyl cyclase (AC) catalyzes cAMP from ATP. This activates protein kinase A (PKE), which results in changes in gene transcription patterns through the phosphorylation of CREB. Similarly, guanylyl cyclase (GC) catalyzes cGMP from GTP, which activates protein kinase G. PDEs hydrolyze cAMP and cGMP, regulating the intracellular levels of cAMP and cGMP and their downstream targets. Relevant CREB target genes include brain-derived neurotrophic factor, corticotrophin-releasing factor, and neuropeptide Y, which are all implicated in SUDs (Wen et al., 2018).

Abbasi, S.-H., Hosseini, F., Modabbernia, A., Ashrafi, M., Akhondzadeh, S., 2012. Effect of celecoxib add-on treatment on symptoms and serum IL-6 concentrations in patients with major depressive disorder: randomized double-blind placebo-controlled study. Journal of affective disorders 141, 308–314.
Abulseoud, O.A., Miller, J.D., Wu, J., Choi, D.-S., Holschneider, D.P., 2012. Ceftriaxone upregulates the glutamate transporter in medial prefrontal cortex and blocks reinstatement of methamphetamine seeking in a condition place preference paradigm. Brain research 1456, 14–21.
Abuse, S., 2022. Mental Health Services Administration. (2021). Key substance use and mental health indicators in the United States: Results from the 2020 national survey on drug use and health (HHS Publication No. PEP21-07-01-003, NSDUH Series H-56). Rockville, MD: Center for Behavioral Health Statistics and Quality. Substance Abuse and Mental Health Services Administration. Retrieved from https://www. samhsa. gov/data.

prevents ethanol-related neuroinflammation (Schneider et al., 2017). The only clinical trial of NAC for AUD found a significant benefit of NAC on drinks per drinking day relative to placebo over time; however, secondary alcohol-related outcomes were null (Morley et al., 2023). There are ongoing clinical trials of NAC for adults and adolescents with AUD (NCT05408247, NCT03707951). Other GLT-1 targeting pharmacotherapies have been investigated preclinically, including ceftriaxone and clavulanic acid, which are beta-lactam antibiotics. Both pharmacotherapies show evidence for reducing alcohol consumption and preference (Alhaddad et al., 2014; Hakami and Sari, 2017; Lee et al., 2013; Qrunfleh et al., 2013).

2.4. Phosphodiesterase (PDE) targets for AUD

Phosphodiesterase (PDE) inhibitors, and particularly PDE-4

Table 1
Summary of neuroimmune treatment studies across substance classes.

Target	Medication	Preclinical Findings	Clinical Findings
Alcohol			
TLR4 antagonist	Naltrexone	↓ ethanol intake, preference, binge-drinking [1]	↓ return to drinking, heavy drinking days [2]
TLR4 antagonist	Naltrexone	↓ binge-drinking [3]	↓ heavy drinking days, drinks per drinking day [4]
TLR3/TRIF inhibitor	Amlexanox	↓ ethanol intake [5]	–
PPARα agonist	Fenobirbate	↓ ethanol intake, preference, self-administration [6, 7, 8]	↓ alcohol craving and drinking (NCT02158273)
PPARγ agonist	Pioglitazone	↓ ethanol intake and preference, self-administration, ethanol-induced reinstatement [6, 9]	Poor safety and tolerability, resulting in terminated clinical trials [10]
Microglial activation inhibition	Minocycline	↓ ethanol intake, preference, self-administration, and ethanol-induced reinstatement [11,12]	No change in subjective response to alcohol, alcohol craving, or serum cytokine levels [13]
Glutamate transporter 1 (GLT-1)	N-acetylcysteine (NAC)	↓ ethanol intake, binge drinking, ethanol-seeking [14, 15]	↓ alcohol consumption [16]
GLT-1	Ceftriaxone	↓ ethanol intake, withdrawal, cue-induced reinstatement [17, 18, 19]	–
GLT-1	Clavulanic acid	↓ ethanol intake [20]	–
PDE-4 inhibitor	Rolipram	↓ ethanol intake, preference, seeking [8, 21–24]	Poor side effect profile
PDE-4 inhibitor	Apremilast	↓ ethanol intake, preference [25,26]	↓ drinks per day, probability of heavy drinking [26]
PDE3A, PDE4, PDE10A, PDE11A inhibitor	Ibudilast	↓ ethanol intake [27]	↓ alcohol craving, heavy drinking days [28,29]
Opioids			
TLR4 antagonist	Naloxone	↓ opioid-induced conditioned place preference, opioid self-administration [30]	–
TLR4 antagonist	Naltrexone	↓ incubation of cue-induced heroin-seeking [31]	–
PPARγ agonist	Pioglitazone	↓ opioid self-administration, withdrawal-related behaviors, drug-induced reinstatement [32–35]	↓ heroin craving, no effect on reinforcing subjective effects of heroin [36]
Microglial activation inhibition	Minocycline	↓ opioid-induced conditioned place preference, priming-induced reinstatement [37,38]	↓ subjective effects of oxycodone in recreational users [39]; no effect on craving or withdrawal in individuals with OUD [40]
Non-selective PDE inhibitor	Propentofylline	↓ withdrawal-related behaviors, opioid-reward [41]	–
PDE3A, PDE4, PDE10A,	Ibudilast	↓ withdrawal-related behaviors [42]	↓ withdrawal ratings, subjective effects of

(*continued on next page*)

Table 1 (*continued*)

Target	Medication	Preclinical Findings	Clinical Findings
PDE11A inhibiotr			oxycodone, craving [43, 44]
Cocaine			
GLT-1	Ceftriaxone	↓ cocaine self-administration, cue- and drug-induced reinstatement [45–49]	Poor side effect profile, requires IV administration
GLT-1	Clavulanic acid	↓ reinforcing effects of cocaine [50]	Completed, but unpublished, clinical trials (NCT03986762, NCT02563769, and NCT04411914)
GLT-1	NAC	↓ cocaine self-administration, cocaine-seeking, drug-induced reinstatement [51–54]	↓ craving; no effect on cocaine use in active users [55,56]
PDE3A, PDE4, PDE10A, PDE11A inhibitor	Ibudilast	↓ drug-induced locomotor sensitization, cocaine self-administration, cue- and drug-primed reinstatement [57,58]	–
PDE4B inhibitor	KVA-D-88	↓ cocaine-mediated reward behaviors [59]	–
Non-selective PDE inhibitor	Pentoxifylline	–	Trend ↓ cocaine use [60]
Microglial activation inhibition	Minocycline	↓ conditioned place preference [61]	–
PPARγ agonist	Pioglitazone	↓ cocaine cue-reactivity [62]	↓ cocaine craving [63]
Methamphetamine			
PDE3A, PDE4, PDE10A, PDE11A inhibitor	Ibudilast	↓ self-administration, stress-induced reinstatement [64, 65]	↓ reward-related subjective effects; no benefit on promoting abstinence [66, 67]
Microglial activation inhibition	Minocycline	↓ conditioned place preference, self-administration, reinstatement [68–70]	–
GLT-1	Ceftriaxone	↓ methamphetamine-seeking [71]	–
GLT-1	NAC	No effect on methamphetamine self-administration or reinstatement [72]	↓ craving [73]

1. Jacobsen et al. (2018); 2. Anton., 2008; 3. Montesinos et al. (2017); 4. Palpacuer (2015); 5. McCarthy et al. (2018); 6. Blednov et al. (2015); 7. Blednov et al. (2016); 8. Ozburn et al. (2020); 9. Fotio et al., 2020, 10. Schwandt et al. (2020); 11. Agrawal et al. (2011); 12. Gajbhiye et al. (2018); 13. Petrakis et al. (2019); 14. Lebourgeois et al. (2018); 15. Schneider et al. (2017); 16. Morley et al. (2023); 17. Alhaddad et al. (2014); 18. Lee et al. (2013); 19. Qrunfleh et al. (2013); 20. Hakami and Sari (2017); 21. Blednov et al. (2014); 22. Franklin et al. (2015); 23. Gong et al. (2017); 24. Hu et al. (2011); 25. Blednov et al. (2018); 26. Grigsby et al. (2023); 27. Bell et al. (2015); 28. Ray et al. (2017); 29. Grodin et al. (2021); 30. Hutchinson et al. (2012); 31. Theberge et al. (2013); 32. de Guglielmo et al. (2017); 33. de Guglielmo et al. (2014); 34. De Guglielmo et al. (2015); 35. Ghavimi et al. (2014); 36. Jones et al. (2018); 37. Arezoomandan and Haghparast (2015); 38. Hutchinson et al. (2008); 39. Mogali et al. (2021); 40. Arout et al. (2019); 41. Narita et al. (2006); 42. Hutchinson et al. (2009); 43. Cooper et al. (2016); 44. Metz et al. (2017); 45. Ward et al. (2011); 46. Bechard et al. (2018); 47. Knackstedt et al. (2010); 48. LaCrosse et al. (2016); 49. Sari et al. (2009); 50. Kim et al. (2016); 51. Ducret et al. (2016); 52. Jastrzębska et al. (2016); 53. Murray et al. (2012); 54. Reichel et al. (2011); 55. LaRowe et al. (2007); 56. LaRowe et al. (2013); 57. Poland et al. (2016); 58. Mu et al. (2021); 59. Burkovetskaya et al. (2020); 60. Ciraulo et al. (2005); 61. Northcutt et al. (2015); 62. Miller et al. (2018); 63. Schmitz et al. (2017); 64. Snider et al. (2013a); 65. Beardsley et al. (2010); 66. Worley et al. (2016); 67. Heinzerling et al. (2020); 68. Attarzadeh-Yazdi et al. (2014); 69. Fujita et al. (2012); 70. Snider et al. (2013b); 71. Abulseoud et al. (2012); 72. Charntikov et al. (2018); 73. Mousavi et al. (2015)..

inhibitors, have been well-studied in preclinical models of AUD. Rolipram, a selective PDE-4 inhibitor, has been shown to reduce ethanol intake, ethanol preference, ethanol seeking, and attenuate abstinence-like behaviors (Blednov et al., 2014; Franklin et al., 2015; Gong et al., 2017; Hu et al., 2011; Ozburn et al., 2020). However, rolipram does not have promise translationally, as it has a poor side effect profile. Apremilast, a partial competitive PDE4 inhibitor, has a better side effect profile than rolipram, and reduces ethanol intake and preference (Blednov et al., 2018; Grigsby et al., 2023). In clinical samples, apremilast reduced the number of drinks per day and the probability of heavy drinking in individuals with an AUD (Grigsby et al., 2023).

My research has focused on ibudilast, a selective PDE inhibitor, with preferential inhibition of PDE3A, PDE4, PDE10A, and PDE11A (Gibson et al., 2006) as a promising treatment for AUD. Ibudilast has been shown to reduce alcohol consumption and craving in both preclinical (Bell et al., 2015) and early-phase clinical studies (Grodin et al., 2021, 2022; Ray et al., 2017). Moreover, a preliminary study found individuals with a pro-inflammatory profile at baseline, indicated by a C-reactive protein (CRP) level of >3, may benefit the most from treatment with ibudilast (Grodin et al., 2023). Specifically, individuals with a pro-inflammatory profile at baseline who were treated with ibudilast drank around 2.8 drinks per drinking day, whereas those with a low level of inflammation at baseline drank around 6.5 drinks per drinking; indicating a substantial benefit of personalizing this treatment to those with an inflammatory profile. Importantly, CRP is an accessible and widely used clinical indicator of inflammation. Therefore, measuring CRP levels as a way to inform patient section can be easily implemented into clinical practice.

3. Opioids

There has been significant interest in neuroimmune therapies as treatments for opioid use disorder (OUD; Table 1). Opioids induce the activation of glia, through the pattern recognition receptor, TLR-4, which is a key mediator of inflammation (Carranza-Aguilar et al., 2022; Hutchinson et al., 2012; Jacobsen et al., 2014). Opioids also interact with microglia within the brain to alter the function of the brain's reward system and contributes to the behavioral effects implicated in continued opioid use (Hutchinson et al., 2007).

3.1. TLR targets for OUD

Studies investigating the neuroimmune modulation of TLRs for OUD have been mostly preclinical. (+)-Naltrexone and (+)-naloxone, which are low-affinity TLR-4 inhibitors, have been shown to block the development of morphine conditioned place preference, attenuate synthetic opioid self-administration, and block cue-induced reinstatement of heroin self-administration (Hutchinson et al., 2012; Theberge et al., 2013). However, these results failed to replicate (Tanda et al., 2016). -

3.2. PPAR targets for OUD

In preclinical studies, pioglitazone, a PPARγ agonist which inhibits the expression of cytokines by microglia, has shown promising effects as an OUD pharmacotherapy. Pioglitazone reduces heroin self-administration, reduces the development of opioid tolerance, attenuates morphine withdrawal symptoms, and reduces drug-induced reinstatement of heroin seeking (de Guglielmo et al., 2014, 2017; De Guglielmo et al., 2015; Ghavimi et al., 2014). In individuals with OUD, pioglitazone did not alter the reinforcing or positive subjective effects of heroin, but did reduce heroin craving (Jones et al., 2018). *3.3 Microglia Targets for OUD.*

Minocycline, an antibiotic which is a microglial inhibitor with anti-

inflammatory properties, has been evaluated preclinically and clinically for OUD. Minocycline reduces morphine-induced conditioned place preference and priming-induced reinstatement (Arezoomandan and Haghparast, 2015; Hutchinson et al., 2008). Initial human laboratory studies found that minocycline reduces the subjective effects of oxycodone in recreational users (Mogali et al., 2014) and healthy volunteers (Mogali et al., 2021); however, in individuals with OUD, minocycline did not alter opioid craving or withdrawal (Arout et al., 2019).

3.3. Phosphodiesterase (PDEs) targets for OUD

PDE inhibitors have also been investigated as treatments for OUD. Propentofylline, a non-selective PDE inhibitor that inhibits TNF-α release and increases GLT-1 expression, suppresses the rewarding effects of morphine (Narita et al., 2006). Ibudilast reduces morphine-induced dopamine release in the nucleus accumbens and morphine withdrawal behaviors (Bland et al., 2009; Hutchinson et al., 2009; Ledeboer et al., 2007). These findings have partially translated in humans; in a two-week inpatient trial of ibudilast for OUD, ibudilast-treated patients had lower ratings of withdrawal during detoxification relative to placebo (Cooper et al., 2016). Recently detoxified patients with OUD treated with ibudilast reported reduced subjective effects of oxycodone and attenuated craving for heroin (Metz et al., 2017). However, no randomized clinical trials have been conducted.

Overall, the promising preclinical findings of neuroimmune pharmacotherapies have not translated to successful clinical trials for individuals with OUD. However, to date, only a limited number of targets have been examined and further proof-of-mechanism studies are required (Butelman et al., 2023).

4. Psychostimulants

4.1. Cocaine

Cocaine's main mechanism of action is through the prevention of dopamine transporter removal of dopamine from synapses, resulting in enhanced dopaminergic transmission (Kalivas, 2022). Importantly, cocaine also affects central and peripheral immune function (Northcutt et al., 2015). A number of clinical studies have identified a pro-inflammatory profile in individuals with a cocaine use disorder (CUD), such that levels of circulating cytokines (monocyte chemoattractant protein-1 (MCP-1), interleukin-1β (IL-1β), IL-6, IL-17, tumor necrosis factor-α (TNF-α), IL-10, and transforming growth factor-α (TGF-α)) are dysregulated (Araos et al., 2015; Iacono et al., 2018; Levandowski et al., 2016; Maza-Quiroga et al., 2017; Moreira et al., 2016; Pedraz et al., 2015).

4.1.1. Glial targets for CUD

The modulation of glial GLT-1 has been widely researched in CUD. Ceftriaxone increases the expression and function of GLT-1 (Lee et al., 2008). In preclinical studies, ceftriaxone reduces cocaine self-administration (Ward et al., 2011) and attenuates cue- and cocaine-primed reinstatement of cocaine-seeking (Bechard et al., 2018; Knackstedt et al., 2010; LaCrosse et al., 2016; Sari et al., 2009). However, ceftriaxone requires intravenous administration, has poor brain penetration, and induces gastrointestinal side effects, which limit its translation to clinical samples (Hadizadeh et al., 2022). Clavulanic acid is also restores GLT-1 expression (Goodwani et al., 2015). Preclinical studies have found that clavulanic acid reduces the reinforcing effects of cocaine (Kim et al., 2016). There have been several completed or ongoing clinical trials of clavulanic acid for CUD (NCT03986762, NCT02563769, and NCT04411914); however, results have yet to be published. NAC, also increases the expression and function of GLT-1; and has been found to reduce cocaine self-administration, cocaine-seeking, and cocaine-induced reinstatement in preclinical studies (Ducret et al., 2016; Jastrzębska et al., 2016; Murray et al., 2012; Reichel et al., 2011). Initial open-label clinical studies showed promise for NAC in increasing treatment retention and reducing use (Mardikian et al., 2007), and in reducing craving during cue-reactivity (LaRowe et al., 2007) and following intravenous cocaine injection (Amen et al., 2011). However, a randomized, double-blind placebo-controlled study of NAC was null (LaRowe et al., 2013). An ongoing randomized clinical trial will evaluate if NAC as a relapse prevention agent in abstinent patients with a CUD (NCT03423667).

4.1.2. Phosphodiesterase (PDE) targets for CUD

Several studies have examined PDE inhibition as a promising target for CUD. In rodents, ibudilast attenuates cocaine-induced locomotor sensitization (Poland et al., 2016), decreases cocaine self-administration (Mu et al., 2021), and reduces prime- and cue-induced reinstatement of cocaine seeking (Mu et al., 2021). Propentofylline, a PDE inhibitor and GLT-1 upregulator, decreases cue- and cocaine-induced reinstatement of cocaine seeking in rodents (Reissner et al., 2014). KVA-D-88, a novel PDE4B inhibits cocaine-mediated reward (Burkovetskaya et al., 2020). Pentoxifylline, a PDE inhibitor, was tested in a pilot clinical trial as a treatment for CUD (Ciraulo et al., 2005). There was a trend towards decreased cocaine use and lower addiction severity scores in the active treatment group compared to placebo (Ciraulo et al., 2005). However, no further clinical trials have been conducted.

4.1.3. Other neuroimmune targets for CUD

Other agents of potential promise for cocaine use disorder treatment include minocycline and pioglitazone. Minocycline suppresses cocaine-induced conditioned place preference (Northcutt et al., 2015), and prevents the development of cocaine sensitization (Chen and Manev, 2011; Chen et al., 2009). Pioglitazone attenuates cocaine cue reactivity in rodents (Miller et al., 2018). In a pilot trial, treatment with pioglitazone reduced cocaine craving and improve white matter integrity in individuals with CUD (Schmitz et al., 2017). There is an ongoing randomized clinical trial of pioglitazone to confirm these preliminary findings (NCT04843046).

4.2. Methamphetamine

Methamphetamine use disorder (MUD) is associated with significant alterations in the immune and neuroimmune systems. In brief, methamphetamine exposure disrupts the blood brain barrier, activates microglia and astrocytes in the brain, alters the expression of proinflammatory cytokines, and allows for the penetration of macrophages and monocytes into the brain (Loftis and Janowsky, 2014).

4.2.1. Phosphodiesterase (PDE) targets for MUD

PDE inhibition may be a promising treatment for MUD. In preclinical studies, ibudilast reduced methamphetamine self-administration (Snider et al., 2013a) and attenuated prime- and stress-induced reinstatement of use (Beardsley et al., 2010). Human laboratory studies found that ibudilast reduced the reward-related subjective effects of methamphetamine (Worley et al., 2016) and attenuated the acute pro-inflammatory effects of methamphetamine administration (Li et al., 2020). However, a randomized clinical trial of ibudilast for MUD found no benefit of the medication on promoting abstinence (Heinzerling et al., 2020). An ongoing clinical trial of ibudilast is evaluating the effects of the drug on neuroinflammation, as measured via positron emission tomography, and cognition in individuals with MUD (NCT03341078).

4.2.2. Glial targets for MUD

Minocycline has shown promise in preclinical studies. Minocycline attenuates methamphetamine-induced conditioned place preference (Attarzadeh-Yazdi et al., 2014; Fujita et al., 2012), blocks priming-induced reinstatement (Attarzadeh-Yazdi et al., 2014), and reduces methamphetamine self-administration (Snider et al., 2013c).

Minocycline has yet to be tested in humans with MUD; however, in healthy volunteers minocycline attenuated the subjective rewarding effects of dextroamphetamine (Sofuoglu et al., 2011).

GLT-1 modulation has also been studied in MUD. Ceftriaxone blocks methamphetamine seeking behavior (Abulseoud et al., 2012). NAC has been efficacious in preclinical studies with cocaine (see above), but not with methamphetamine (Charntikov et al., 2018). However, a randomized trial NAC to treat MUD found significant reductions in craving following treatment (Mousavi et al., 2015). In sum, there are no FDA-approved treatments for stimulant use disorders and outpatient clinical trials have proven challenging to execute and to detect medication effects in this disorder.

5. Conclusion and future directions

Overall, the use of neuroimmune modulators as pharmacotherapies for SUDs holds great promise and may provide an effective and much-needed treatment option for individuals with SUDs. For AUD, promising pharmacotherapies include NAC, ibudilast, and apremilast. For OUD, most treatments have failed to translate to clinical samples. For CUD, clavulanic acid and pioglitazone may be promising treatments, but clinical trials are ongoing. For MUD, NAC may show promise, although the preclinical literature is mixed, and additional clinical trials are warranted. This review did not discuss nicotine or cannabis, given that nicotine is thought to be immunosuppressive (Geng et al., 1996; Sopori, 2002), and cannabis may be anti-inflammatory (Graczyk et al., 2021).

Of note, several pharmacotherapies have been tested for multiple SUDs (e.g., ibudilast, NAC, minocycline). Multiple classes of substances have been shown to alter the immune system (Crews et al., 2017; Lacagnina et al., 2017), and, as such, it may be unsurprising that neuroimmune modulators have been tested across substances. However, some pharmacotherapies have been effective for one substance while proving non-effective for other substances. These differences may be the result of different mechanisms of immune-related action for each class of substance. This may also be the result of methodological differences between substance classes, subject sample differences in severity and location, and/or study designs.

It is clear that many pharmacotherapies which have showed positive results in preclinical studies have failed to translate to clinical samples. While there are many reasons for which medications fail to translate, one explanation for this failure may be due to the heterogeneity of SUDs. In this context, it is likely that medications, including neuroimmune modulators, may be effective for subgroups of patients, and ineffective or even iatrogenic for other subgroups of patients. It is plausible that individuals with a SUD may need an underlying profile of increased inflammation in order to see an effect of a neuroimmune modulator (Gano et al., 2023; Ioannou et al., 2021). In my own research, we have shown that the effect size of ibudilast to treat AUD in individuals with elevated CRP at baseline, indicative of elevated inflammation, is medium-to-large (Grodin et al., 2023), whereas the effect size if individuals are collapsed across inflammatory profiles is small (Grodin et al., 2022). This approach has also been proposed in the context of major depression disorder (MDD) (Drevets et al., 2022). In MDD, individuals with elevations in proinflammatory cytokines at baseline show a better medication response to several neuroimmune pharmacotherapies (Abbasi et al., 2012; Raison et al., 2013; Savitz et al., 2018; Uher et al., 2014). Of note, findings related to elevated proinflammatory profiles have been limited to *post hoc* analyses. In order to move the field towards a precision-medicine approach, it will be critical to conduct hypothesis-driven studies where individuals are stratified on baseline levels of inflammation and randomized controlled trials are conducted (Drevets et al., 2022). Relatedly, it will be critical to identify which markers of inflammation are the most sensitive to quantify the level of immune dysregulation (e.g., CRP, cytokine levels). Moreover, additional moderators, including sex, age, stress, poly-substance use, and comorbid depression, are associated with inflammation (Beurel et al., 2020; De Cecco et al., 2019; Russell and Lightman, 2019; Takahashi and Iwasaki, 2021) and may play a critical role in response to neuroimmune medications in individuals with SUDs (Butelman et al., 2023) and will need to be investigated.

Finally, it is possible that neuroimmune therapies may be good candidates for combination pharmacotherapy treatments (Matt, 2021) or for adjunctive treatments alongside psychotherapy. Combined pharmacotherapy and cognitive behavioral therapy is more effective than pharmacotherapy with usual care across SUDS (Ray et al., 2020). Combining pharmacotherapies may allow for the targeting of more than one dysfunctional neurotransmitter system or allow for the treatment of comorbid psychiatric and medical disorders; this combination may result in an additive effect to decrease craving and substance use (Lee and Leggio, 2014). Several pharmacotherapy combinations have been tested in animal models (Goodwani et al., 2015; Israel et al., 2021; Stopponi et al., 2013); however, combination pharmacotherapies with neuroimmune treatments have yet to be tested in clinical samples.

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CRediT authorship contribution statement

Erica N. Grodin: Conceptualization, Funding acquisition, Resources, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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